

The Association between Coagulation Parameters, C-Reactive Protein, D-Dimer and In-Hospital Mortality of Covid-19 Patients with Suspected Pulmonary Embolism

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Abstract:

COVID-19 is a respiratory disease with severe cardiovascular complications, one of them is pulmonary embolism (PE). Studies have shown many contributing factors related to mortality of hospitalized COVID-19 patients that developed pulmonary embolism. This study aimed to find the association between coagulation parameters (PT and APTT), C-reactive protein (CRP), and D-dimer with in-hospital mortality of COVID-19 patients with suspected PE. COVID-19 patients in Ulin General Hospital Banjarmasin who met the clinical criteria of suspected PE, assessed with clinical scorings (Well's score for PE and Padua prediction score for venous thromboembolism), and receiving anticoagulant therapy recorded in medical records were included in this study. A total of 91 patients were included, with most patients were female (59.3%), average age of 53.36 years, average BMI of 25.82 kg/m², having normal electrocardiogram (79.1%), with history of hypertension (56%), and no histories of smoking (94.5%), diabetes mellitus (70.3%), heart failure (93.4%), coronary artery disease (96.7%), and chronic lung disease (95.6%). As much as 39.57% patients with suspected PE was deceased during the course of hospitalization. Unadjusted analysis showed significant increased levels of PT, APTT, and CRP, in deceased patients compared to those discharged alive (mean 14.62 vs 11.91 seconds, 42.94 vs 28.57 seconds, and 98.19 vs 47.01 mg/dL, respectively; p value < 0.01), and a non-significant increased level of D-dimer (mean 10.89 mg/L; p = 0.09). Multivariate logistic regression showed non-significant associations between PT, APTT, D-dimer, and CRP with in-hospital mortality (p values of 0.06, 0.14, 0.52, and 0.23, respectively). In conclusion, there is no association between coagulation parameters, CRP, and D-dimer levels with in-hospital mortality in COVID-19 patients with suspected PE. A further study with a larger sample size is needed to see the role of laboratory findings in predicting in-hospital mortality in COVID-19 patients with suspected PE.

Keywords: COVID-19; In-hospital mortality; Pulmonary embolism

Introduction

Corona Virus Disease 2019 (COVID-19) is an emerging respiratory disease that originated in mainland China since 2019, and as per January 2023, Indonesia had over 6 million confirmed cases with 2.39% mortality rate.¹ The spectrum of this disease ranges from flu-like symptoms to acute respiratory distress syndrome caused by SARS-CoV-2. This disease also constitutes many additional cardiovascular ailments; one of them is pulmonary embolism (PE).² Autopsy finding by Wichmann et al. showed that 58% of COVID-19 patients had PE as the direct mortality cause.³ Meta analysis by Liao et al shows that COVID-19 patients with PE overall incidence and mortality rate can reach up to 15.3% and 45.1%, respectively.⁴ Many studies showed laboratory findings such as prothrombin time (PT) and activated partial thromboplastin time (APTT) prolongation and elevated levels of C-reactive protein (CRP) and D-dimer were found in deceased COVID-19 patients that developed PE.⁵⁻⁸ This shows that laboratory findings mentioned above may have a role associated with in-hospital mortality in COVID-19 patients with PE.

Every confirmed COVID-19 patient with suspected PE should have computed tomography pulmonary angiography (CTPA) to confirm the PE. If the CTPA is not available, transesophageal echocardiography (TEE) and lower extremities Doppler examinations can be obtained to find DVT and right ventricular dysfunction which is highly associated with PE. Clinical scoring can be used if there are any limitations to use devices above, such as Wells criteria to determine PE suspicion.⁹ Ulin General Hospital is the largest tertiary referral hospital in South Borneo, Indonesia that serves to care COVID-19 patients in this province, particularly patients from moderate to critical state of this disease. However, technical limitation to undertake CTPA in Ulin

General Hospital imposes a challenge in diagnosis of PE in COVID-19 patients. This limitation can increase the mortality and morbidity in COVID-19 patients with suspected PE. It became imperative to find other kinds of modality to predict and deter mortality caused by PE in COVID-19 patients. The laboratory findings such as PT, APTT, CRP, and D-dimer can serve as risk factor for clinicians to be more aware in mortality in COVID-19 patients with suspected PE. These laboratory findings are also commonly obtained in hospital with limited radiologic modality in Indonesia. Hence, this study aimed to assess the clinical characteristics and the associations between coagulation parameters (PT and APTT), CRP, and D-dimer, and in-hospital mortality in COVID-19 patients with suspected PE in Ulin General Hospital.

Research Method

The design of this study used a retrospective cohort approach on hospital medical records. Subjects of this study were COVID-19 patients (confirmed using reverse transcriptase-polymerase chain reaction (RT-PCR) method) with suspected PE in Ulin General Hospital Banjarmasin since June 2020 until January 2021. Suspicion of PE was judged by clinical history, laboratory findings, clinical scoring (Well's score for PE¹⁰ and Padua prediction score for VTE¹¹) and the use of thromboprophylaxis anticoagulant therapy (unfractionated heparin, low molecular weight heparin, or fondaparinux). The ethical clearance was approved by the Ethics Committee on Medical Research in the Medical Faculty of Universitas Lambung Mangkurat and Ulin General Hospital with document number of 518/KEPK-FK ULM/EC/I/2021 and 02/I-Reg Riset/RSUDU/21, respectively.

Data extracted from the medical records included the variables of age, sex, smoking history, diabetes mellitus (DM), hypertension

(HT), heart failure (HF), coronary artery disease (CAD), electrocardiogram (ECG) findings, history of lung disease, body mass index (BMI), Well's score for PE, Padua prediction score for VTE, PT, APTT, CRP, D-dimer and in-hospital mortality outcome. The dependent variables were age, sex, smoking history, diabetes mellitus (DM), hypertension (HT), heart failure (HF), coronary artery disease (CAD), ECG findings, history of lung disease, body mass index (BMI), Well's score for PE, Padua prediction score for VTE, PT, APTT, CRP, D-dimer and the independent variable was in-hospital mortality. The data were analyzed using SPSS program to reveal the descriptive characteristics of each variable as clinical profile, and bivariate logistic regression was used to analyze the difference between those patients who were deceased and not deceased. Multivariate logistic regression was used to analyze the association between PT, APTT, CRP and D-dimer to in-hospital mortality outcome. The results were considered significant if the *p* value was < 0.05.

Results

This study included 91 COVID-19 patients with suspected PE. We found the mean age of the patients is 53.36 ± 11.69 years. Most of the patients are female (54%). The majority of them has no history of smoking, DM, HF, CAD, history of lung disease and most of the ECG findings are normal sinus rhythm. The most common abnormal ECG finding is sinus tachycardia. Majority of the patients had hypertension (*n* = 51, 56%). The mean value of BMI of the patients was 25.82 ± 5.03 kg/m². The scoring of suspected PE was done using three-tier model Well's score for PE and Padua prediction score for VTE. The mean value of Well's score of the patients is 3.4 ± 0.99 while Padua prediction score for development of venous thromboembolism (VTE) showed the

mean score of 5.26 ± 1.3 . The clinical profile of the patients who are deceased and discharged alive was also summarized in **table 1**. The laboratory findings of the patients in **table 2** shows PT, APTT, CRP, and D-dimer values of the patients. Coagulation parameters (PT and APTT) had mean value of 12.98 ± 3.64 seconds and 34.26 ± 19.56 seconds, respectively. The mean CRP level of the patients is 67.26 ± 84.97 mg/dL, while the mean D-dimer level is 7.46 ± 12.86 mg/L.

Bivariate logistic regression analysis showed significant increased levels of PT, APTT, CRP, and D-dimer in deceased patients compared to those discharged alive (mean 14.62 vs 11.91 seconds, 42.94 vs 28.57 seconds, and 98.19 vs 47.01 mg/dL, respectively; *p* value < 0.01), and a non-significant increased level of D-dimer (mean 10.89 mg/L; *p* = 0.09). Multivariate logistic regression in **table 3** showed non-significant associations between PT, APTT, CRP, and D-dimer with in-hospital mortality (*p* values of 0.06, 0.14, 0.52, and 0.23, respectively).

Discussion

This study found that there is no significant association between prolonged PT and APTT toward in-hospital mortality in COVID-19 patients with suspected PE (*p* = 0.06, 95% CI = 0.996–1.459 and *p* = 0.14, 95% CI = 0.987–1.095, respectively). However, other research found that coagulopathy is commonly found in these patients, both PT and APTT are expected to be prolonged primarily in acute phase of the infection.¹² Wichmann et al. autopsy found 2 of 12 deceased COVID-19 patients with confirmed PE patients had prolonged PT and APTT.³ A study by Zhou et al shows there was a significant association between prolonged PT and death in COVID-19 patients.¹³ Prolonged PT and APTT in COVID-19 patients were found to be the independent predictor of

thrombotic event that can lead to PE.¹⁴ However, Tang et al. research on coagulation parameter's association to outcome showed a significant association between PT prolongation and poor prognosis while APTT showed no significancy. This study also showed 74% of deceased patients met the

criteria of disseminated intravascular coagulation.¹⁵ The condition of coagulopathy can show a sign of hypercoagulable states, as there is an increased prothrombotic factors such as von Willebrand factor, factor VIII, fibrinogen, D-dimer, and prothrombotic microparticles.¹⁴

Table 1. Clinical profile of COVID-19 patients with Suspected Pulmonary Embolism in Ulin General Hospital

Characteristics	All Patients N = 91 (100%)			Deceased N = 36 (39,57%)			Discharged Alive N = 55 (60.43%)			p value
	N	%	Mean±SD	N	%	Mean±SD	N	%	Mean±SD	
Age			53.36±11.69			53.19±10.12			53.47±12.7	0.91
Sex										
Male	37	40.7		25	69.4		29	52.7		0.12
Female	54	59.3		11	30.6		26	47.3		
Smoking										
Yes	5	5.5		9	25		3	5.5		0.98
No	86	94.5		27	75		52	94.5		
DM										
Yes	27	29.7		12	33.3		15	27.3		0.54
No	64	70.3		24	66.7		40	72.7		
HT										
Yes	51	56		23	63.9		28	50.9		0.22
No	40	44		13	36.1		27	49.1		
HF										
Yes	6	6.6		2	5.6		4	7.3		0.75
No	85	93.4		34	94.4		51	92.7		
CAD										
Yes	3	3.3		2	5.6		1	1.8		0.35
No	88	96.7		34	94.4		54	98.2		
ECG										
Abnormal	19	20.9		9	25		10	18.2		0.44
Normal sinus rhythm	72	79.1		27	75		45	81.8		
CLD										
Yes	4	4.4		2	5.6		2	3.6		0.67
No	87	95.6		34	94.4		53	96.4		
BMI (kg/m ²)			25.82±5.03			26.47±5.64			25.39±4.58	0.32
Well's Score			3.4±0.99			3.81±1.31			3.13±0.59	<0.01
Padua Prediction Score			5.26±1.3			5.81±1.37			4.91±1.12	<0.01

BMI: Body mass index; CAD: Coronary artery disease; CLD: Chronic lung disease; DM: Diabetes mellitus; ECG: Electrocardiogram; HF: Heart failure; HT: Hypertension

Table 2. Laboratory findings of COVID-19 patients with Suspected Pulmonary Embolism in Ulin General Hospital

Laboratory findings (unit)	Normal value	All Patients N = 91 (100%)	Deceased N = 36 (39,57%)	Discharged Alive N = 55 (60.43%)	p value
		Mean±SD	Mean±SD	Mean±SD	
PT (seconds)	10-14	12.98±3.64	14.62±4.26	11.91±2.71	0.00
APTT (seconds)	21-35	34.26±19.56	42.94±28.12	28.57±6.47	0.01
CRP (mg/dL)	0-0.6	67.26±84.97	98.19±99.77	47.01±67.28	0.01
D-Dimer (mg/L)	0.25-0.5	7.46±12.86	10.89±18.17	5.21±6.98	0.09

APTT: Activated partial thromboplastin time; CRP: C-reactive protein; PT: Prothrombin time

Table 3. Association between PT, APTT, CRP, and D-dimer in COVID-19 patients with suspected PE in Ulin General Hospital

Variable	p value	95% CI	OR
PT	0.06	0.996–1.459	1.205
APTT	0.14	0.987–1.095	1.039
CRP	0.52	1–1.012	1.006
D-dimer	0.23	0.98–1.086	1.032

APTT: Activated partial thromboplastin time; CRP: C-reactive protein; PT: Prothrombin time

There was no significant association between elevated level of CRP and in-hospital mortality in COVID-19 patients with suspected PE in this study ($p = 0.52$, 95% CI = 1-1.012). A study by Nur'amin et al. showed no significant relationship between CRP levels and severe manifestation of COVID-19 (OR 0.85 95%; CI 0.34-2.09, $p=0.72$)¹⁶, even though other studies revealed the opposite. A meta-analysis by Sahu et al. showed that deceased COVID-19 patients have significantly higher CRP compared to the discharged ones, with common complications seen are ARDS, shock, and coagulopathy.¹⁷ A study by Kho et al. also found increased CRP in COVID-19 patients with pulmonary embolism with median value of 189 mg/L.¹⁸ Poyiadji et al. found an above normal CRP level on admission in COVID-19 patients with PE, and a significant rise of the value after 2 days of admission, which indicates a higher CRP level as susceptibility of developing PE in COVID-19 patients.⁵ Tomlins et al. study shows CRP as a predictor of mortality in COVID-19 patients, with median value of 77 mg/L in its association with progressive inflammation and end organ damage.¹⁹ A study in Wuhan, China by Deng et al. showed there is a significant increase of CRP levels in deceased COVID-19 patients compared to the surviving ones. The CRP levels in deceased patients remained high even after treatments such as antiviral and corticosteroid therapy.⁷ Increased level of CRP in COVID-19 patients with PE may also indicate a superimposed secondary bacterial infection and mortality in these patients. CRP

is an inflammatory biomarker and commonly found to be elevated in COVID-19 patients, particularly the critical ones. This biomarker has a role in pathogen clearance through the complement system and increased phagocytosis during acute phase of COVID-19 infection.¹⁷ Hence, CRP is an important inflammatory marker in COVID-19 patients with PE.²⁰

This study found no significant association between D-dimer level and in-hospital mortality in COVID-19 patients with suspected PE ($p = 0.23$, 95% CI = 0.98-1.086). Meanwhile, there are many studies that showed significant association between D-dimer level and poor outcomes in hospitalized COVID-19 patients. Leonard-lorant et al. found that there is a significant increase of D-dimer level in COVID-19 patients with confirmed PE, as much as 30% of 106 patients with median value 15.385 mg/L.²¹ The increased D-dimer levels on admission can also determine the risk of developing PE in COVID-19 patients, Garcia-olive et al. found that there was a higher probability of PE as much as 1.7 times after 3 days, 2 times after 6 days, 2.4 times after 9 days, and 2.4 times after 12 days since the first D-dimer evaluation.²¹ Zhou et al. research showed that an increase D-dimer level greater than 0.001 mg/L in admission is associated with increased odds of in-hospital mortality as much as 18 times.¹³ A case study in New York by Griffin et al. found 3 COVID-19 patients with confirmed PE, all of them had elevated D-dimer level above normal value on admission.²³ Tang et

al. also found that D-dimer level is also significantly higher on admission in deceased COVID-19 patients with PE.⁸ A meta-analysis by Suh et al. found the overall incidence rate of confirmed PE in COVID-19 patients were 16.5% and D-dimer levels were found significantly higher in this population with sensitivity and specificity as much as 96% and 10% respectively.²⁴ As fibrin degradation product released in by activation of coagulation cascade during systemic inflammatory response syndrome (SIRS), D-dimer was found to be associated with poor prognosis and high mortality in COVID-19 patients with VTE, with minimal value of 0.1 mg/L.¹²

The result this study found no association between PT, APTT, CRP, and D-dimer levels with in-hospital mortality in COVID-19 patients with suspected PE, however, these laboratory findings may still be associated with in-hospital mortality in these patients as other studies suggest. The limitation of this study lies on its sample size, therefore, there has to be a continuation of this study that capture a larger sample size in Ulin General Hospital.

Conclusions

This study found no significant association between the levels of coagulation parameter (PT and APTT), CRP, and D-dimer with in-hospital mortality of COVID-19 patients with suspected PE despite opposite results from other studies. A further study with a larger sample size is recommended in order to confirm the association between these variables.

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